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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,157	05/10/2001	Douwe Molenaar	P 278405 990012 BT-CIP	3863

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EXAMINER
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RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 09/09/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/852,157	MOLENAAR ET AL.
	Examiner Delia M. Ramirez	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on \_\_\_\_.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_ is/are allowed.

6) Claim(s) 1-15 is/are rejected.

7) Claim(s) \_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_ is: a) approved b) disapproved by the Examiner.

    If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a) All b) Some \* c) None of:

        1. Certified copies of the priority documents have been received.

        2. Certified copies of the priority documents have been received in Application No. \_\_\_\_.

        3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    \* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

    a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_.

4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_.

5) Notice of Informal Patent Application (PTO-152)

6) Other: \_\_\_\_.

**DETAILED ACTION**

***Status of the Application***

Claims 1-15 are pending.

***Priority***

1. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to GERMANY 19912384.5 filed on 3/19/1999. It is noted that certified copies of the priority documents have not been received.
2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/436,362 filed on 11/09/1999.

***Claim Objections***

3. Claim 5 is objected to because of the following informalities: for clarity, it is suggested that the term “nucleotide sequence coding for said malate:quinone oxidoreductase” be replaced with “nucleotide sequence encoding said malate:quinone oxidoreductase” or “polynucleotide encoding said malate:quinone oxidoreductase”. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, Second Paragraph***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 2-10 are indefinite in the recitation of “the improvement of claim #”, “the improvement of any one of claims #” or “the improvement according to ...” since claim 1, from which claims 2-7 are dependent, is directed to a process. For examination purposes, it will be assumed that the intended meaning of the term is “the process of claim #.... wherein ...”. Correction is required.

7. Claims 8 and 15 are indefinite in the recitation of “production of L-lysine” since there is no recitation of L-lysine in the Markush group recited in claims 7 and 14, from which claims 8 and 15 depend, respectively. For examination purposes, it will be assumed that claim 8 is drawn to the method of any one of claims 1-4 wherein L-lysine is produced. Similarly, for examination purposes, claim 15 will be assumed to be directed to the process of claim 11 wherein L-lysine is produced. Correction is required.

8. Claim 9 is indefinite in the recitation of “the gene coding for dihydrodipicolinate synthase” as there is no antecedent basis for the gene. For examination purposes, it will be assumed that the intended term is “a gene ....”. Correction is required.

9. Claim 11 (claims 12-15 dependent thereon) is indefinite in the recitation of “fermenting the bacteria produced in step a” for the following reasons. Step a) refers to the amplification of a malate:quinone oxidoreductase gene in bacteria and not to the production of bacteria. For examination purposes, it will be assumed that the term’s intended meaning is “fermenting the L-

amino acid producing bacteria wherein a malate:quinone oxidoreductase gene has been amplified, as described in step a)". Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a process for the production of any L-amino acid by fermenting a genus of coryneform bacteria wherein the activity of a genus of malate:quinone oxidoreductases is enhanced in said bacteria by any means. Claim 2 is directed to the process of claim 1 with the added limitation that the activity of the malate:quinone oxidoreductases should be enhanced by over-expression of their corresponding genes. Claims 3-4 are drawn to the process of claim 1 with the added limitation that said coryneform bacteria have been further treated such that (1) any enzyme of an L-amino acid biosynthetic pathway is enhanced in any way or (2) any pathway which reduces the biosynthesis of an L-amino acid has been eliminated. Claim 5 is directed to the process of any of claims 1-4 with the added limitation that the activity of the malate:quinone oxidoreductases is enhanced by transforming the coryneform bacteria with a plasmid vector

comprising a polynucleotide encoding said oxidoreductases. Claim 6 is directed to the process of claim 5 with the added limitation that the plasmid vector is pRM17. Claims 7-8 are directed to the process of any one of claims 1-4 with limitations in regard to the amino acids to be produced. Claim 9 is directed to the process of claim 7 with the added limitation that a genus of genes encoding dihydronicotinate synthases is over-expressed in the bacteria. Claim 10 is directed to the process of claim 7 with the added limitation that a genus of DNA fragments associated with S-(2-aminoethyl)-cysteine resistance are amplified in the bacteria. Claim 11 is drawn to a process for producing a genus of L-amino acids by fermenting a genus of coryneform bacteria wherein a genus of malate:quinone oxidoreductase genes are amplified in said bacteria. Claim 12 is directed to the process of claim 10 wherein said bacteria is further modified to enhance the activity of a genus of genes associated with the biosynthetic pathway of any L-amino acid. Claim 13 is directed to the process of claim 11 wherein said bacteria is transformed with the plasmid vector pRM17. Claims 14-15 are directed to the process of claim 11 with limitations in regard to the amino acids to be produced.

While the specification discloses the production of L-lysine and L-threonine by transforming *C. glutamicum* with a plasmid containing the malate:quinone oxidoreductase (mqo) of *C. glutamicum* strain ATCC 13032, the specification is silent in regard to (1) malate:quinone oxidoreductase genes from other sources or other coryneform bacteria, (2) the production of other L-amino acids as claimed, (3) methods to enhance the intracellular activity of malate:quinone oxidoreductases, such as structurally modifying the coding region of the corresponding genes to encode malate:quinone oxidoreductases with enhanced activity as compared to the wild-type counterparts or structurally modifying transcriptional control elements

in the corresponding genes, (4) the identity and structure of genes encoding any enzyme of any coryneform bacterium wherein said enzyme is associated with the biosynthetic pathway of any L-amino acid, (5) methods to enhance the activity of any enzyme from any coryneform bacterium involved in the biosynthetic pathway of any L-amino acid, (6) which metabolic pathways have to be eliminated to reduce the formation of an L-amino acid, (7) the identity and structure of genes associated with the metabolic pathways which have to be eliminated to reduce the formation of an L-amino acid, (8) the structure of other genes encoding dihydroadipicollinate synthases, (9) the structure of other DNA fragments associated with S-(2-aminoethyl)-cysteine resistance, and (10) the critical structural elements required in any DNA encoding malate:quinone oxidoreductase.

The argument can be made that the malate:quinone oxidoreductase genes from other organisms, as well as other genes required to practice the claimed invention from other organisms, can be isolated by sequence comparison with the mqo gene from *C. glutamicum*. However, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a  $\beta$ -ketoacyl synthase into a malonyl decarboxylase and completely eliminates  $\beta$ -ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two

naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, in addition to methods of enhancing activity of proteins as recited in the claims, an extremely large number of DNA/protein structures that are required to practice the claimed method have not been adequately described. The specification discloses only one method to increase the activity of one malate:quinone oxidoreductase in one microorganism, which is insufficient to put one of skill in the art in possession of the attributes and features of the claimed method. Thus, one of skill in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

12. Claims 6 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel vectors. Since the vectors are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The vectors required to practice the claimed invention are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. §

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112 may be satisfied by a deposit of the vectors, i.e. plasmid pRM17. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these vectors should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited the organisms comprising the required vectors but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

- a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;
- b. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
- c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
- d. the deposit will be replaced if it should ever become non-viable.

13. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-15 are directed to a method for the production of any L- amino acid wherein said method comprises cultivating a coryneform microorganism which has been modified to enhance the intracellular activity of malate:quinone oxidoreductase, including amplification of the gene encoding said malate:quinone oxidoreductase. While the specification provides examples in which L-lysine and L-threonine have been produced by cultivating a *C. glutamicum* transformed with a plasmid comprising the *C. glutamicum* malate:quinone oxidoreductase gene (*mqa*) such that the intracellular activity of such oxidoreductase is increased by over-expression of the corresponding DNA, copending application 10/118325 (common assignee Degussa AG; US publication 20030044943) teaches that attenuation of the *C. glutamicum* *mqa* gene in *C. glutamicum* results in the production of L-amino acids. See the entire document. The specification in copending application 10/118325 even discloses the production of L-lysine by attenuating such *C. glutamicum* gene (Example 3). In view of the conflicting and opposing teachings of both specifications, and the lack of additional information in the instant application, it is unclear as to whether the method disclosed in the instant application is operable. In view of the fact that it cannot be determined if the claimed invention can be practiced as disclosed, one cannot reasonably conclude that Applicants have provided sufficient guidance to enable the claimed invention.

14. Even if Applicants can overcome the enablement rejection applied above in regard to the operability of the claimed method, the following rejection would also apply. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing L-lysine or L-threonine in *C. glutamicum* by cultivating *C. glutamicum* which has been transformed with a plasmid comprising the *C. glutamicum* malate:quinone oxidoreductase gene such that the intracellular activity of said *C. glutamicum* malate:quinone oxidoreductase is increased by over-expression of the corresponding DNA, does not reasonably provide enablement for a (1) method for producing any L-amino acid by cultivating coryneform bacteria which have been modified in any way to enhance the intracellular activity of any malate:quinone oxidoreductase or wherein any malate:quinone oxidoreductase gene is amplified, (2) a method as described in (1) wherein the coryneform bacteria have been further modified in any way to enhance the activity of any enzyme from any organism associated with the biosynthetic pathway of any L-amino acid, or (3) the method as described in (1) wherein the coryneform bacteria has been further modified in any way to eliminate any metabolic pathway which reduces the formation of any L-amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in regard to the large number of genes and or DNA fragments required to practice the claimed invention as well as methods to enhance/eliminate the activity of many unknown proteins encompassed by the claims. As indicated above, while there is disclosure of a method for the production of L-lysine and L-threonine by cultivation of a *C. glutamicum* bacterium transformed with a plasmid comprising the *C. glutamicum* ATCC 13032 mqo gene such that there is over-expression of the *C. glutamicum* malate:quinone oxidoreductase, the specification fails to disclose (1) the structures of other genes encoding malate:quinone oxidoreductases and methods to enhance their activity, (2) genes encoding any enzyme of any coryneform bacterium involved in the biosynthetic pathway of any L-amino acid and methods to enhance their activity, (3) pathways that reduce the formation of any L-amino acid and methods to eliminate them as well as genes associated with such pathways, (4) other genes encoding dihydrodipicolinate synthases, (5) the structure of other DNA fragments associated with S-(2-aminoethyl)-cysteine resistance, (6) the critical structural elements required in any DNA encoding malate:quinone oxidoreductase, and (7) production of other L-amino acids as encompassed by the claims.

While one could argue that the specification is enabling for the full scope of the claimed invention since one could isolate other genes required to practice the claimed method by structural homology using the structures of genes disclosed in the specification or the prior art, the state of the art, as evidenced by Bork, Broun et al., Seffernick et al., Van de Loo et al. and Witkowski et al., clearly teaches the unpredictability of determining whether structural homologs are also functional homologs. See discussion above. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural

elements required in DNAs encoding the enzymes and proteins recited in the claims, the lack of knowledge in regard to how to enhance/eliminate activity of the recited proteins, and the unpredictability of the prior art in regard to assigning function based on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

#### ***Double Patenting***

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-2, 4-5, 11 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of copending Application No. 10/178219 (common inventor Bettina Mockel). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined

claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 10 of copending Application No. 10/178219 is directed in part to a fermentation process for the production of L- lysine, which uses a coryneform microorganism modified such that it contains a pyruvate oxidase (poxB) gene, wherein the expression of said gene has been reduced or eliminated, and a malate:quinone oxidoreductase gene (mqo) wherein said gene is over-expressed or amplified. Pyruvate oxidase is responsible for the conversion of pyruvate directly to acetate and CO<sub>2</sub>. Claims 1-2 of the instant application are directed to a fermentation process for producing L-amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 4 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with metabolic pathways that reduce the formation of any L-amino acid is eliminated. Claim 5 of the instant application is directed in part to the process of any one of claims 1, 2 or 4 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform microorganism with a plasmid comprising the DNA encoding said oxidoreductase. Claim 8 of the instant application is directed in part to the process of any one of claims 1, 2, or 4 wherein the amino acid produced is L-lysine.

Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Claim 15 of the instant application is directed to the process of claim 11 wherein L-lysine is produced. Since pyruvate oxidase is part of the pathway which directs pyruvate away from amino acid biosynthesis in order to synthesize acetate and CO<sub>2</sub>, reduction or elimination of expression of a gene encoding pyruvate oxidase would constitute a modification which switches off a metabolic pathway which reduces the formation of L-amino acids. Therefore, claim 10 of copending Application No. 10/178219 would anticipate claims 1-2, 4-5, 11 and 15 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-2, 4-5, 11 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of copending Application No. 10/375355 (common assignee Degussa AG). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 14 of copending Application No. 10/375355 is directed in part to a fermentation process for the production of L-lysine which uses a coryneform microorganism modified such that it contains a citrate lyase E (citE) gene, wherein the expression of said gene has been reduced or eliminated, and a malate:quinone oxidoreductase gene (mqo), wherein the expression of said gene is enhanced or over-expressed. The citE gene encodes one of the subunits of citrate lyase, which is the enzyme responsible for the conversion of citrate to oxaloacetate and acetate. Claims 1-2 of the instant application are directed to a fermentation process for producing L-amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 4 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with metabolic pathways that reduce the formation of any L-amino acid is eliminated. Claim 5 of the instant application is directed in part to the process of any one of claims 1, 2 or 4 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform microorganism with a plasmid comprising the DNA encoding said oxidoreductase. Claim 8 of the instant application is directed in part to the process of any one of claims 1, 2, or 4 wherein the amino acid produced is L-lysine. Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Claim 15 of the instant application is directed to the process of claim 11 wherein L-lysine is produced. Since citrate lyase is part of the pathway which directs citrate

away from the biosynthesis of those amino acids which are synthesized from  $\alpha$ -ketoglutarate, succinyl-CoA, and fumarate, reduction or elimination of expression of a gene encoding citrate lyase would constitute a modification which switches off a metabolic pathway which reduces the formation of L-amino acids. Therefore, claim 14 of copending Application No. 10/375355 would anticipate claims 1-2, 4-5, 11 and 15 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-2, 4-5, 11 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 09/804073 (common assignee Degussa AG). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 15 of copending Application No. 09/804073 is directed in part to a fermentation process for the production of L-lysine which uses a coryneform microorganism modified such that it contains a phosphoenolpyruvate (PEP) carboxylase (pepC) gene, wherein the expression of said gene has been attenuated or eliminated, and a malate:quinone oxidoreductase gene (mqo),

wherein the expression of said gene is enhanced or over-expressed. The pepC gene encodes PEP carboxylase, which is the enzyme responsible for the conversion of PEP to oxaloacetate.

Claims 1-2 of the instant application are directed to a fermentation process for producing L-amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 4 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with metabolic pathways that reduce the formation of any L-amino acid is eliminated. Claim 5 of the instant application is directed in part to the process of any one of claims 1, 2 or 4 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform microorganism with a plasmid comprising the DNA encoding said oxidoreductase. Claim 8 of the instant application is directed in part to the process of any one of claims 1, 2, or 4 wherein the amino acid produced is L-lysine. Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Claim 15 of the instant application is directed to the process of claim 11 wherein L-lysine is produced. Since PEP carboxylase is part of the pathway which directs PEP away from the biosynthesis of those amino acids which are synthesized from  $\alpha$ -ketoglutarate, succinyl-CoA, and fumarate, reduction or elimination of expression of a gene encoding PEP carboxylase would constitute a modification which switches off a metabolic pathway which

reduces the formation of L-amino acids. Therefore, claim 15 of copending Application No. 09/804073 would anticipate claims 1-2, 4-5, 11 and 15 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 1-2, 4-5, 11 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of copending Application No. 09/770688 (common assignee Degussa AG). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 14 of copending Application No. 09/770688 is directed in part to a fermentation process for the production of L-lysine which uses a coryneform microorganism modified such that it contains a citrate lyase E (citE) gene, wherein the expression of said gene has been reduced or eliminated, and a malate:quinone oxidoreductase gene (mqr), wherein the expression of said gene is enhanced or over-expressed. The citE gene encodes one of the subunits of citrate lyase, which is the enzyme responsible for the conversion of citrate to oxaloacetate and acetate. Claims 1-2 of the instant application are directed to a fermentation process for producing L-

amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 4 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with metabolic pathways that reduce the formation of any L-amino acid is eliminated. Claim 5 of the instant application is directed in part to the process of any one of claims 1, 2 or 4 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform microorganism with a plasmid comprising the DNA encoding said oxidoreductase. Claim 8 of the instant application is directed in part to the process of any one of claims 1, 2, or 4 wherein the amino acid produced is L-lysine. Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Claim 15 of the instant application is directed to the process of claim 11 wherein L-lysine is produced. Since citrate lyase is part of the pathway which directs citrate away from the biosynthesis of those amino acids which are synthesized from  $\alpha$ -ketoglutarate, succinyl-CoA, and fumarate, reduction or elimination of expression of a gene encoding citrate lyase would constitute a modification which switches off a metabolic pathway which reduces the formation of L-amino acids. Therefore, claim 14 of copending Application No. 09/770688 would anticipate claims 1-2, 4-5, 11 and 15 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1-2, 4-5, 11 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 09/938540 (common inventor Bettina Mockel). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 18 of copending Application No. 09/938540 is directed in part to a fermentation process for the production of L-lysine which uses a coryneform microorganism modified such that it contains a catabolite control protein A (ccpA1) gene, wherein the expression of said gene has been reduced or eliminated, and a malate:quinone oxidoreductase gene (mqo), wherein the expression of said gene is enhanced. Catabolite control protein A is one of the enzymes involved in glucose repression of carbon source utilization genes. Claims 1-2 of the instant application are directed to a fermentation process for producing L-amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 4 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone

oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with metabolic pathways that reduce the formation of any L-amino acid is eliminated. Claim 5 of the instant application is directed in part to the process of any one of claims 1, 2 or 4 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform microorganism with a plasmid comprising the DNA encoding said oxidoreductase. Claim 8 of the instant application is directed in part to the process of any one of claims 1, 2, or 4 wherein the amino acid produced is L-lysine. Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Claim 15 of the instant application is directed to the process of claim 11 wherein L-lysine is produced. Since catabolite control protein A is part of the pathway which limits glucose transport into the cell, reducing or eliminating its synthesis would allow additional carbon source to be intracellularly available for amino acid production. Therefore, reduction or elimination of expression of a ccpA1 gene would constitute a modification which switches off a metabolic pathway which reduces the formation of L-amino acids. Therefore, claim 18 of copending Application No. 09/938540 would anticipate claims 1-2, 4-5, 11 and 15 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1-2, 4-5, 11 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-17 of copending Application No. 09/733386 (common inventor Bettina Mockel). An obviousness-type double

patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 16-17 of copending Application No. 09/733386 are directed in part to a fermentation process for the production of L-lysine which uses a coryneform microorganism modified such that it contains a zwa2 gene, wherein the expression of said gene has been reduced or eliminated, and a malate:quinone oxidoreductase gene (mqa), wherein the expression of said gene is enhanced by over-expression or amplification. According to the specification of copending Application No. 09/733386, the zwa2 gene from *C. glutamicum* is associated with the biosynthesis of L-amino acids and its attenuation results in the production of L-amino acids.

Claims 1-2 of the instant application are directed to a fermentation process for producing L-amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 4 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with metabolic pathways that reduce the formation of any L-amino acid is eliminated. Claim 5 of the instant application is directed in

part to the process of any one of claims 1, 2 or 4 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform microorganism with a plasmid comprising the DNA encoding said oxidoreductase. Claim 8 of the instant application is directed in part to the process of any one of claims 1, 2, or 4 wherein the amino acid produced is L-lysine. Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Claim 15 of the instant application is directed to the process of claim 11 wherein L-lysine is produced. Since according to the specification of copending Application No. 09/733386, attenuation of the zwa2 gene results in L-amino acid production, claims 16-17 of copending Application No. 09/733386 would anticipate claims 1-2, 4-5, 11 and 15 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 1-3, 5, and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of copending Application No. 09/796431 (common assignee Degussa AG). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 24 of copending Application No. 09/796431 is directed in part to a fermentation process for the production of L-glutamic acid which uses a coryneform microorganism modified such that it contains a glycerol-3-phosphate dehydrogenase (gpsA) gene, wherein the expression of said gene has been enhanced, and a malate:quinone oxidoreductase gene (mqo), wherein the expression of said gene is enhanced, over-expressed or amplified. According to the specification of copending Application No. 09/796431, enhancement or over-expression of the gpsA gene from *C. glutamicum* results in the production of L-amino acids. Claims 1-2 of the instant application are directed to a fermentation process for producing L-amino acids which uses a coryneform microorganism modified such that the activity of malate:quinone oxidoreductase is enhanced in any way or by over-expressing the gene encoding said oxidoreductase. Claim 3 of the instant application is directed in part to a fermentation process for the production of L-amino acids which uses a coryneform microorganism modified such that it contains a malate:quinone oxidoreductase gene which is over-expressed or amplified, and wherein the expression of any gene associated with any L-amino acid biosynthetic pathway is enhanced. Claim 5 of the instant application is directed in part to the process of any one of claims 1, 2 or 3 wherein the activity of the oxidoreductase is enhanced by transforming the coryneform bacterium with a plasmid comprising the DNA encoding said oxidoreductase. Claim 11 of the instant application is directed to a process for producing an L-amino acid using a coryneform microorganism modified such that a malate:quinone oxidoreductase gene is amplified in said microorganism. Since according to the specification of copending Application

No. 09/796431, enhancement of the expression of the gpsA gene results in L-amino acid production, claim 24 of copending Application No. 09/796431 would anticipate claims 1-3, 5 and 11 of the instant application as written.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

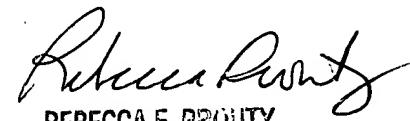
23. No claim is in condition for allowance.
24. It is noted that if the references cited by the Examiner are too long, only relevant pages will be enclosed with the instant Action.
25. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.
26. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.  
Patent Examiner  
Art Unit 1652

DR  
September 3, 2003

  
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